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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/073,596
Filing Date: May 06, 1998
Appellant(s): STEINMAN ET AL.

Leigh W. Thorne, Ph.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/09/10 appealing from the Office action mailed 2/23/10.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 99, 101, 104-113, 116, 120, and 142-145.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the

appeal is taken (as modified by any advisory actions) is being maintained by the examiner.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

PANCHOLI, P., et al. *Immunology*. 1992;76:217-224.

INABA, K., et al. *Journal Experimental Medicine*. 1990;172:631-640.

STEINMAN, R.M., et al. *Annals N.Y. Academy Science*. 1988;546:80-90.

MARKOWICZ, S. and ENGELMAN, E.G. *Journal Clinical Investigation*. 1990;85:955-961.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 99, 101, 104-113, 116, 120, 142-145 are rejected under 35 U.S.C. 102(a) as being anticipated by Pancholi et al. (1992).

Pancholi et al. teaches a pharmaceutical composition comprising human dendritic cells (DCs) pulsed with tuberculosis antigens (see particularly page 218, last paragraph).

The reference clearly anticipates the claimed invention.

Regarding product-by-process claims, MPEP 2113 states:

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), and

"The Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature" than when a product is claimed in the conventional fashion. *In re Fessmann*, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir.1983).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 99, 101, 104-113, 116, 120, 142-145 are rejected under 35 U.S.C. 103(a) each as being unpatentable over Inaba et al. (1990) in view of Steinman et al. (1988) and Markowicz and Engleman (1990).

Inaba et al. teaches mouse DCs cultured with antigen (see particularly Table 1) that process and express the modified antigen (Table 6, as demonstrated by the cell's ability to prime T cells). The reference further teaches that said pulsed DCs could be useful in "a new approach to immunization" because of their natural adjuvant properties and because the dendritic cell would naturally select the antigen that could be presented on any particular MHC (see page 639, last paragraph).

The reference differs from the claimed invention only in that it does not teach DCs matured in GM-CSF nor human DCs.

Steinman et al. teaches the enrichment and culturing of both mouse and human immature DCs found in blood, as well as bone marrow, (see pages 81-83) and that, "maturation is driven by factors such as IL-1 and GM-CSF" (see page 83). The reference further teaches that "GM-CSF is critical in mobilizing

active DCs at the onset of a cell-mediated immune response" (see page 88).

Markowicz and Engleman teach that, "GM-CSF … profoundly affects the morphology and viability of DCs isolated from peripheral blood. GM-CSF not only promotes DC survival but also induces DC differentiation mobile, reversibly adherent cells with long-branched projections. DC cultured in GM-CSF survive for up to 6 weeks and retain their ability to stimulate the proliferation of T cells in allogeneic and autologous MLR" (Abstract). Note that absent GM-CSF these properties were lost (see Figure 5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add GM-CSF to a cell culture of DCs such as the mouse cultures of Inaba et al. and Steinman et al. or the human cultures of Steinman et al. and Markowicz and Engleman. The ordinarily skilled artisan would have added GM-CSF to DC cultures given the teachings of Steinman et al., that, DC "maturation is driven by factors such as IL-1 and GM-CSF", etc. and Markowicz and Engleman, that, "GM-CSF … profoundly affects the morphology and viability of DCs isolated from peripheral blood…". Accordingly, the GM-CSF-cultured DCs as claimed are obvious in view of the combined prior art.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 99, 101, 104-113, 116, 120, 142-145 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a written description rejection for the introduction of new matter into the claims.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, a method step of allowing culture, "for a time sufficient to allow the antigen to bind to the dendritic cells and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 120 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically, it is unclear whether or

not the actions of the claim are actually intended to be method steps. If so, then the steps must be separated and indented as is required of all method steps.

(10) Response to Argument

A. Appellant argues that support for the claimed invention is found in the '612 priority application. As set forth in the final Office action the benefit of priority has been denied:

The instant application is a continuation in part of U.S. Application Nos. 07/981,357, filed 11/25/1992, and 07/861,612, filed 4/01/92. However, the applications do not disclose the invention of the instant claims. First note that the method step employed in instant Claim 101 comprising, "treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors", is not found in the '612 application. Further, neither the '612 nor the '357 applications disclose the cells being cultured with an antigen as is recited in the last step of Claims 101 and 120. Accordingly, the benefit of priority to said applications is denied. The priority date of the instant application is the filing date of parent application 08/040,677 which is 3/31/1993.

Note that the claims have been amended to recite "modified" antigens and a final "wherein" method step of allowing culture "for a time sufficient to allow the antigen to bind to the dendritic cells and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells". This step has not been found in either of the '612 nor '357 applications.

Note that the culturing wherein clause of Claim 101 has been amended to recite an active culturing step.

Applicant's arguments, filed 12/11/09, have been fully considered. Applicant now cites page 22, lines 10-20 of the '612 application in support.

The cite does not provide adequate support for the claimed step. First, it encompasses the production of "antigen activated DCs" and not the production of the mature DCs of Claims 101, 120, and new Claim 45. Mature DCs and antigen-activated DCs are not synonymous. In the instant context it appears that antigen-activation occurs before maturation (which requires additional culture after activation). There is also no disclosure of the modified antigen of the claims. Also note that no support is cited in the '357 application.

Applicant cites original Claims 17 and 36 in the '612 application.

Regarding original Claims 36 and 17 of the '612 application, Claim 17, from which Claim 36 depends, does not recite several of the limitation of instant Claim 101, e.g., mature DCs "derived from an *in vitro* culture of an enriched and expanded population of proliferating DC precursors" nor the "treating the tissue source comprising DC precursors to increase the proportion of DC precursors" nor "culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain cell aggregates comprising proliferating dendritic cell precursors", etc. Applicant has picked a limitation out of it's

original context and attempted to use it here to support the amended claims. Again, no support is cited in the '357 application.

Applicant cites the method disclosed at page 7, line 22 through page 8, line 6 in the '612 application.

A review of the method shows that it does not include the first treating step of Claim 101, nor the final culturing step, nor the wherein clause of the claim. Neither does the cite disclose the modified antigens of the claims.

Applicant cites page 8, lines 15-19 in the '612 application in support of the modified antigens of the claims.

As set forth above, the modified antigens of the instant specification are disclosed only in the context of antigen-activated DCs. And in the instant context it appears that antigen-activation occurs before maturation (which requires additional culture after activation). Thus, antigen-activated DCs are not synonymous with mature DCs.

Accordingly, the benefit of priority is again denied.

Also note again that no support has been cited in the 07/981,357 application.

Appellant cites the specification at pages 8-10 and now refers to the cells of the claims as "antigen-activated mature dendritic cells", **a term that is not found anywhere in any of**

the applications. It appears that Appellant is attempting to subtly modify the claimed invention so that it fits modern immunological terms and encompass concepts that were not known almost two decades ago when the parent applications were filed. Particularly note the paragraph spanning pages 9 and 10 of the instant application. While the cite discloses "antigen-activated" dendritic cells the cite does not disclose that these are the mature dendritic cells of the instant claims.

35 U.S.C. §102 – Anticipation, B. Appellant argues that Pancholi et al. does not anticipate the claimed cells because the claimed cells are cultured *in vitro* in GM-CSF which was, "surprisingly found to promote the proliferation *in vitro* of precursor dendritic cells" whereas the dendritic cells of the reference were isolated from blood. At the time of the invention GM-CSF was well known dendritic cell culture additive. Indeed, see the BACKGROUND OF THE INVENTION wherein GM-CSF is referred to repeatedly as a dendritic cell culture additive. And as will be noted repeatedly later, GM-CSF's proliferative properties are irrelevant to the claimed invention, a composition comprising mature dendritic cells.

Regardless, Appellant argues that the dendritic cells of the reference are not the dendritic cells of the instant claims because the dendritic cells of the instant claims are better stimulators of T cells *in vitro*. Appellant cites Figure 2 of the reference in support of the argument.

A review of the reference shows that the isolated dendritic cells of the reference did indeed stimulate T cells *in vitro*.

Figure 2(a) shows that the dendritic cells were better stimulators of T cells than were monocytes/macrophages or B cells. Figure 2(b) shows that purified dendritic cells were capable of stimulating T cells. The skilled artisan would also know that it is inappropriate to try to directly compare the experiments of the reference to the experiments of the instant specification. It must be noted that the general conclusions of both sets of experiments are the same, antigen loaded dendritic cells stimulate T cells; but to try to draw conclusions based on the details of the experiments, e.g., cell ratios, is not scientifically sound. Such a comparison would require the holding of all parameters constant, e.g., antigens, antigen concentrations, antigen loading conditions, all culture and assay conditions, buffers, etc., to see if the *in vitro* derived cells were indeed fundamentally different than were the isolated from *in vivo* dendritic cells. No such experiments have been performed, thus Appellant's conclusion has no scientific support. In all likelihood, the dendritic cells of the reference were a mixture of immature and mature dendritic cells wherein the mature dendritic cells activated T cells just as do the mature dendritic cells of the instant claims. It would also seem that if Appellant's line of reasoning were to be accepted, and the *in vitro* derived dendritic cells of the claims were found to be a different type of dendritic cell than the dendritic cells of the reference, then the scope of the claimed cell type would be extremely limited, i.e., the dendritic cells of the claims would be limited to only those dendritic cells produced by the specific method of the instant claims and no other.

35 U.S.C. §103 – Obviousness, C. Appellant argues that, "None of the references, either alone or in any combination, teach or suggest that the use of GM-CSF to culture dendritic cell precursors *in vitro* produces an enriched and expanded population of proliferating dendritic cell precursors that can be used to produce a large population of mature dendritic cells expressing modified antigen."

Such a showing is clearly not required. The motivation used to combine references need not be the motivation of the Inventors.

Appellant argues that Markowicz and Engleman teach away from the claimed invention because the reference teaches that GM-CSF in dendritic cell culture results in a stable, not proliferating, culture.

Appellant's argument might be persuasive if the claims were drawn to a method of producing mature dendritic cells, but they are not. Indeed, claims drawn to specific methods of producing mature dendritic cells have been allowed. The Examiner's burden is simply to determine whether the teachings of the combined references would result in the claimed product, and to further determine if a motivation to combine the references can be found. In this case the answer is yes and yes. Regarding the arguments concerning proliferating dendritic cell precursors, they are irrelevant to the product of the instant claims which is a composition comprising mature dendritic cells.

Appellant argues that Steinman et al. teaches away from the claimed invention, "because it states that GM-CSF has a role *in vivo* in **maturation** of cells in certain tissues and proposes that GM-CSF may be involved in **mobilizing** DCs at the onset of a cell-mediated immune response" (emphasis by Appellant).

It would seem that GM-CSF's role in "**maturation**" would provide sufficient motivation for including GM-CSF in a dendritic cell culture for the production of mature dendritic cells. And again, Appellant's arguments regarding dendritic cell precursor proliferation are irrelevant because the claims are drawn to a composition comprising mature dendritic cells.

Appellant argues, "The claimed cells differ from previously reported cells, for example, in their ability to take up antigen even after extended periods of culture."

If the claimed dendritic cells had been "previously reported" they would be rejected under 35 U.S.C. §102. The claimed composition of mature dendritic cells has been rejected as obvious in view of the combined references of the rejection.

Appellant argues, "As further evidence of nonobviousness, Appellants note that the Examiner previously withdrew an obviousness rejection over the cited Inaba reference for the stated reason that "an objective and quantifiable difference between the DCs of the prior art and the DCs of the instant claims was established (the inability of the DCs of Inaba et al. to capture antigen after several days of culture)"".

Appellant should also have noted that the rejection that was withdrawn was over Inaba et al. in view of Aldovini et al., whereas the instant rejection is over Inaba et al. (1990) in view of Steinman et al. (1988) and Markowicz and Engleman (1990). Accordingly, that rejection is unrelated to the instant rejection.

Appellant concludes with a reiteration of the argument that the culture of dendritic cell precursors in GM-CSF results in dendritic cell precursor proliferation.

Appellant's argument is noted. But as set forth previously, the claims are drawn to a composition comprising mature dendritic cells, not a composition comprising proliferating dendritic cell precursors or method of producing dendritic cells.

35 U.S.C. §112, first paragraph – Written Description, D.

Appellant cites page 5, lines 20-27; page 34, line 34 – page 35, line 3; page 36, lines 31-33; and page 34, lines 16-20, in support of the claimed limitation, "for a time sufficient to allow the antigen to bind to the dendritic cells and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells".

A review of the cites does not reveal adequate written support for the claimed limitation. First note that the dendritic cells of the limitation are mature dendritic cells because prior to maturation of said cells in the steps of the claims the claims recite only dendritic cell precursors.

Page 5 does not disclose a mature dendritic cell "processing" or "expressing" an antigen. Neither does page 34, line 34 - page 35, line 3, nor page 36, lines 31-33, disclose a mature dendritic cell "processing" or "expressing" an antigen. While page 34, lines 16-20, disclose the processing of antigen, said processing is not disclosed as being done by a mature dendritic cell nor is any "modified antigen" "expression" disclosed.

35 U.S.C. §112, second paragraph – Indefiniteness, E.

Appellant argues that because the clauses of Claim 120 are separated by semicolons the claim is not indefinite.

As set forth in the rejection, it is unclear whether or not the actions of the claim are actually intended to be method steps. If so, then the steps must be separated and indented as is required of all method steps. MPEP 608.01(m) states that claim element of steps should be separated by a line indentation. This means that each step should both begin on a separate line *and* be indented. In this instance the possible steps neither begin on a separate line nor are they indented. Accordingly, it is unclear whether the clauses of the claim actually encompass method steps.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/G.R. Ewoldt/
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